REMARKS

Claims 1-3, 8-10, and 18-20 are pending, claims 4-7, 11-17, and 21-26 having been withdrawn by the Examiner pursuant to 37 C.F.R. 1.142 § (b), and cancelled by applicants' Amendment A of 01 February 2002.

Applicants thank the Examiner for withdrawing, in response to applicants' Amendment A, the claim objections and rejections under 35 U.S.C. § 112 ¶¶ 1 and 2, as listed in paragraphs 4-8 of of Examiner's Office Action of 22 May 2002.

Applicants also thank the Examiner for the telephonic interview of 03 July 2002, wherein all outstanding issues, except for the 35 U.S.C. § 112 ¶ 1 *enablement* rejection with respect to pharmaceutical compositions were effectively resolved. Applicants were additionally informed at that time that Examiner Hunt would be leaving the PTO and transferring this prosecution case to a new Examiner, but that written notes of the telephonic interview would be placed in the file to facilitate fairness and continuity in the examination.

Claims 3 (Amended) and 8 (Amended) have been further responsively amended, as per the telephonic interview of 03 July 2002. Specifically, dependant claims 3 (Amended) and 10 (Amended) have been further amended by deleting the phrase "binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)," in the interest of facilitating prosecution.

Additionally, dependent claims 3 (Amended) and 10 (Amended) have been further amended to recite a single *species* of the respective *genera* of independent claims 1 (Amended), and 8 (Amended).

Applicants submit, attached hereto, an AFFIDAVIT of Gail Clinton (including supporting figures and references), and an AFFIDAVIT of Edward Neuwelt (including supporting figures and references) in confirmation of the ***in vivo*** utility as described, taught and enabled in applicants' originally filed specification.

Finally, new *independent* claims 22 and 23, fully supported by the originally filed specification, have been added. No new matter has been added.

Rejections under 35 U.S.C. § 112 ¶ 2

The Examiner rejected claims 3 and 10, under 35 U.S.C. § 112 ¶ 2, as *indefinite* in the recitation of a site that is "at least in part distinct," where the metes and bounds thereof would not be clear (Office Action of 22 May 2002 at para 9).

Furthermore, as discussed in the telephonic interview of 03 July 2002, the Examiner alleges that there is no direct support in the specification for such a distinction in binding sites between the instant polypeptides and HERCEPTIN® anyway.

While applicants disagree with the Examiner's position (as discussed at page 11-12 of applicants' Amendment A of 01 February 20002), applicants have nonetheless responsively further amended claims 3 (Amended) and 10 (Amended) by deleting the phrase "binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)" from these dependent claims, in the interest of facilitating prosecution.

Additionally, dependent claims 3 (Amended) and 10 (Amended) have been further amended to recite a single *species* of the respective *genera* of independent claims 1 (Amended) and 8 (Amended).

Applicants, therefore, respectfully request withdrawal of Examiner's 35 U.S.C. § 112 ¶ 2 rejection with respect to claims 3 (Twice amended) and 10 (Twice amended).

Rejections under 35 U.S.C. § 112 ¶ 1

The Examiner rejected claims 1-3, 8-10, and 18-20, under § 112 ¶ 1, as lacking *enablement* in that **(i)** "the specification, while being enabling for an isolated peptide comprising SEQ ID NO:1, and or SEQ ID NO:2, does not reasonably provide enablement for any isolated peptide having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or about 350-419 amino acids from SEQ ID NO:2," including **(ii)** which further do not bind to the epitope bound by HERCEPTIN®" as a new grounds of rejection (Office Action of 22 May 2002 at para 10).

Applicants thank the Examiner for the associated enablement analysis under the *Wands* factors (*Id*).

Applicants, however, respectfully traverse the Examiner's enablement rejection with respect to **(i)** above, because this aspect of the rejection, as discussed and agreed to in the telephonic interview of 03 July 2002, was ***already*** addressed by the narrowing claim amendments of applicant's responsive Amendment A of 01 February 2002. In that Amendment applicants responsively amended the claims herein to recite a requirement that the encoded polypeptides must comprise "***contiguous***" sequences of SEQ ID NOs:1 and 2. Additionally, conforming functional language was recited "wherein the polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1} (*see* Amendment A of 01 February 2002 at page 9, including the specification support cited therein). Furthermore, these responsive amendments of Amendment A of 01 February 2002 were *precisely* those upon which the Examiner ***allowed*** the corresponding divisional application encoding-DNA claim restriction group (now issued as **U.S. Patent 6,414,130**). Therefore, applicants assume that the real basis of the Examiner's present rejection lies in **(ii)** above, which appropriately pertains solely to claims 3 and 10, the only claims having disputed the HERCEPTIN® epitope language.

Accordingly, as described above with respect to Examiner's 35 U.S.C. § 112 ¶2 indefiniteness rejection, and as discussed in the telephonic interview of 03 July 2002, applicants have responsively further amended dependant claims 3 (Amended) and 10 (Amended) by deleting the phrase "binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)," in the interest of facilitating prosecution.

Additionally, again as discussed above, dependent claims 3 (Amended) and 10 (Amended) have been further amended to recite a single *species* of the respective *genera* of independent claims 1 (Amended), and 8 (Amended).

Applicants, therefore, respectfully request withdrawal of Examiner's 35 U.S.C. § 112 ¶1 *enablement* rejection with respect to claims 1 (Amended), 2 (Amended), 3 (Twice amended), 8 (Amended), 9 (Amended), 10 (Twice amended), and 18-20 (all Amended).

Additional Rejections under 35 U.S.C. § 112 ¶ 1

The Examiner also maintained the rejection of claims 18-20 under § 112 ¶1 as lacking *enablement* with respect to the use of the subject polypeptides as "pharmaceutical compositions," because of the general "level of predictability of *in vivo* therapy" (*citing* Dillman et al., *J. Clin. Onco.* 12:1497-1555, 1997, and Dermer, *Bio/Technology* 12:320, 1994), and in view of an alleged lack of "guidance or evidence" that any such encoded polypeptides, including ECDIIIa or p68HER-2, would have "anti-tumor activity, or why one of skill in the art would expect such a function to induce anti-tumor activity" (Office Action of 01 August 2001 at pages 12-14).

Essentially, and as discussed in the telephonic interview of 03 May 2002, the Examiner remained uncertain about the therapeutic significance of the anchorage-independent (in soft agar) cancer cell growth experiments described at page 13 of the originally filed patent application involving SKOV-3 and 17-3-1 carcinoma cells, especially where applicants did not provide copies of supportive references (all cited within the original specification) cited by applicants (*see* Office Action of 22 May 2002 at p. 9).

Applicants maintain and reaffirm the arguments presented in applicants' responsive Amendment A of 01 February 2002 and respectfully, but emphatically traverse Examiner's enablement rejection with respect to *in vivo* utility of the subject polypeptides and pharmaceutical compositions. ***First***, the anchorage-independent model used by applicants is regarded in the art as highly indicative of *in vivo* utility. ***Second***, applicants and applicants' collaborators have performed additional *in vitro* and ***in vivo*** studies that entirely confirm the therapeutic utility as originally described, taught and enabled in applicants' originally filed specification.

First, the *in vitro* cell culture soft agar assay used by applicants (*see* Specification at page 13, lines 5-23, and Figure 7) is a widely recognized model system for human cancer (DiFore et al.,

Science 237:178-182, 1987; Hudziak et al., *Proc. Natl. Acad. Sci. USA* 84:7159-7163, 1987; and Baasner et al., *Oncogene* 13:901-911, 1996; all cited in the original subject patent application, and all of record in this prosecution file as **EXHIBIT A** of the Affidavit of Dr. Edward Neuwelt which is being contemporaneously filed with the instant responsive Amendment B), and thus inhibition of such anchorage-independent growth in this system is, within the relevant art, taken as *substantial* proof of not only a well-established *in vivo* utility, but also a specific, credible and substantial *in vivo* utility. This is especially true where the therapeutic *target* HER-2 receptor is already a ***bona fide* clinical target** of the Herceptin™ the FDA-approved humanized monoclonal antibody, and where herstatin, unlike Herceptin™, is a naturally occurring protein having a high degree of specificity, and binding affinity.

Second, applicants submit **two** AFFIDVITS, attached hereto, in full confirmation of the therapeutic utility of the subject polypeptides, as originally disclosed, taught and enabled in applicants' originally filed specification.

AFFIDAVIT OF GAIL CLINTON:

The Affidavit of Gail Clinton (attached hereto) describes ***two*** sets of experimental data using models, techniques and cell lines that were available in the art at the time of filing of said patent application, to further confirm and illustrate the *in vivo* therapeutic efficacy of herstatin as originally disclosed and enabled by the soft agar cell growth experiments and other teachings therein. The ***first*** data set relates to herstatin's efficacy in inhibiting a variety of additional human cancer cell lines that over-express HER-2 and/or the EGF receptor, and further shows that herstatin's efficacy is as good or better than that of Herceptin™, the clinically approved humanized anti-HER-2 monoclonal antibody (*see* Affidavit of Gail Clinton, attached hereto).

The ***second*** data set relates to herstatin's ***in vivo*** stability, and its ***substantial in vivo*** efficacy in *nude* mice in inhibiting xenografts of MCF7/HER-2 human breast cancer cells in nude mice. Specifically, **the subject polypeptides have substantial *in vivo* efficacy in inhibiting the growth**

of xenografts of MCF7/HER-2 human breast cancer cells in nude mice (*see* **FIGURES 3** and **4** of Affidavit of Gail Clinton, attached hereto).

AFFIDAVIT OF EDWARD NEUWELT:

The Affidavit of Edward Neuwelt describes experiments conducted using the art-recognized *in vivo* human tumor model; namely, human U87MG injected into ***nude*** **rats** (*see* Affidavit of Edward Neuwelt, attached hereto). U87MG is a standard human glioblastoma cancer cell line that expresses HER-2 and the EGF receptor (*Id*). Human glioblastoma is typically an aggressive cancer, and is refractory to therapy. Significantly, **herstatin expression inhibited tumor growth and significantly enhanced survival of rats with intra cerebral U87 gliomas**.

In summary, herstatin has equal or better efficacy than Herceptin™, both *in vitro* and *in vivo* against a clinically validated target (HER-2 receptor) and validated models of human cancers. Recombinant herstatin is stable when injected into mice, consistent with its natural occurrence in particular tissues. Herstatin has therapeutic efficacy ***in vivo*** as originally described, taught and enabled in the above-identified patent application.

Applicants, therefore, respectfully request withdrawal of the Examiner's § 112 ¶1 *enablement* rejection with respect to claims 18-20 (all Amended).

New Claims

Applicant's have added new claims 21 and 22, drawn to isolated polypeptides ***consisting*** of the amino acid sequences of SEQ ID NO:1 and SEQ ID NO:2. Support for these new claims is found throughout the originally filed specification, and in particular at Figure 5, Example 9, and at page 23, lines 29-30, and Figure 5C, which recite and show, respectively, that "the ECDIIIa peptide bound to intact 17-3-1 cells at **nM** concentrations." Thus the degree of binding was/is detectable in the *nanomolar* range (*i.e.*, corresponding to a binding constant equal to or greater than 10^8 M^{-1}). Additionally, the specification is replete with references to 'binding' and 'high-affinity binding' and recites the intent to disclose novel high-affinity *binders* (*e.g.*,: the specification at page 1, line 30; at

page 2 , line 26; at page 6, line 24 (in relation to the binding data Figure 5); at page 7, line 9 (in relation to the binding data of Figure 6)).

Therefore, applicants have fully enabled new claims 21 and 22, which in contrast to independent claims 1 and 8, do not, **and need not**, recite functional language with respect to binding affinity, because they recite *consisting* of, rather than *comprising*.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request allowance of the "clean" claim set (claims 1 (Amended), 2 (Amended), 3 (Twice amended), 8 (Amended), 9 (Amended), 10 (Twice amended), 18-20 (all Amended), and new claims 22 and 23), provided herein above.

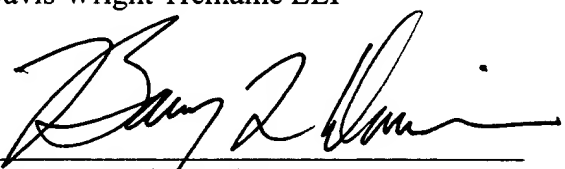
The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

No new matter has been added.

Entry of the Amendment is respectfully requested.

Respectfully submitted,

Davis Wright Tremaine LLP



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APPENDIX A

("marked up" claims, corresponding to those prior pending claims that have been amended herein)

3. (Twice Amended) The isolated polypeptide of claim 1, wherein the isolated polypeptide consists of SEQ ID NO:1 [binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)].

10. (Twice Amended) The isolated polypeptide of claim 8, wherein the isolated polypeptide consists of SEQ ID NO:2 [binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)].